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Positively framed risk information in patient information leaflets reduces side effect reporting: A double-blind randomised controlled trial.

Abstract

Background: Many medication side effects are the result of a psychologically mediated "nocebo effect", triggered by negative expectations.

Purpose: This study investigated if changing how side effect information is framed in patient information leaflets (PILs) reduces symptom reporting.

Methods: 203 healthy volunteers aged 18 or over were recruited from Dec 1 2015 to Dec 5 2016 into a double-blind randomised controlled trial carried out at the Clinical Research Facility at King's College Hospital. King's Clinical Trial Unit randomised participants (stratified by gender) to receive a PIL for "a well-known tablet available without prescription" that used standard side effect risk information (e.g. 'Common, 1 in 10 people will be affected') or positively framed wording (e.g. 'Uncommon, 90% of people will not be affected'). After reading their PIL, participants took the tablet (a placebo) and completed symptom reports one hour later. The main outcomes included the number of participants who attributed symptoms to the tablet, and the number and severity of attributed symptoms.

Results: 101 participants were assigned the standard PIL and 102 the positive framed PIL. Significantly more standard PIL participants attributed symptoms to the tablet (n=55, 54.5%) compared to positively framed PIL participants (n=40, 39.2%), OR=0.66, 95% CI[0.46 to 0.93]. Positive framing did not significantly reduce the total number (p=.148) or severity (p=.149) of symptoms attributed to the tablet.

Conclusion: Positive framing reduced the likelihood of participants attributing nocebo-induced side effects to the tablet. Work is needed to assess the effectiveness in a patient population.

Trial registration: ISRCTN47470030

Key words: positive framing, side effects, risk communication, nocebo, placebo

Side effects are commonly reported to medications, however many are non-specific and not related to the physiological action of the medication (1,2). These non-specific side effects may arise through a nocebo effect (3), defined as the experience of unpleasant symptoms in response to an inert exposure (4). It is important to try and reduce patients' experience of side effects as they can result in both physical and psychological strain on patients. Patients may choose to not take their medication as directed, affecting their health (5) and causing financial consequences for the health services (6).

Nocebo effects are commonly reported in clinical trials, where up to 25% of participants receiving an inert, control tablet report side effects (3). They are also common outside of the laboratory. For example, although high rates of side effects have been attributed to statins among primary care patients (7), clinical trials have found side effect rates to be roughly similar in patients allocated statins and those allocated a sham tablet (8,9). A recent trial has also shown that the rates of side effects reported to statins are much higher when patients know they are receiving statins, rather than when they are blind to their treatment allocation (10). 'Statin intolerance' may therefore be mediated by a nocebo effect, exacerbated by negative expectations generated through patient information leaflets and also adverse media coverage (11). Similar effects have also been proposed for other surprisingly high rates of side effect reporting to medications (12-14).

A recent systematic review by our team of the factors that contribute to nocebo effects supported the importance of negative expectations as an underlying mechanism (15). Patients who expect symptoms are particularly at risk of reporting them. Although expectations are affected by multiple factors, one source that is readily amenable to change are the patient information leaflets (PILs) that accompany every medication given out by pharmacists and which are read by at least 70% of patients when prescribed new medication (16). Side effect

information in PILs has long been a source of concern for some researchers who find it excessive, inconsistent, and often poorly presented (17).

Evidence suggests that what symptoms are mentioned in a PIL can affect side effect rates (18). More subtly, the way side effect risks are framed may also have an impact. Positively framing the risk in terms of the number of people who will not be affected has been shown to result in lower expectations of side effects than negatively framing risk in terms of the number who will be affected (19). O'Connor et al. (20) reframed the information given to participants about side effect risk following an influenza vaccination and found a significant decrease in side effects when using positive framing. O'Connor et al's (20) work has never been replicated, however the Medicine and Healthcare products Regulatory Agency (MHRA) recommends that framing should not be used in PILs, as patients may perceive it as "a marketing ploy"(21). We are unaware of any evidence which supports that assertion.

We tested whether positively framing side effect risk in a PIL reduces nocebo induced side effects and whether it affects satisfaction with or perceived credibility of the PIL. Our hypotheses were as follows:

1. There will be a significant difference in the number of people who attribute symptoms to the tablet between the two conditions
2. There will be a significant difference in the number of symptoms attributed to the tablet between the two conditions
3. There will be a significant difference in the severity of symptoms attributed to the tablet between the two conditions
4. There will be a significant difference in participant-rated satisfaction with the information between the two conditions

5. There will be a significant difference in participant-rated credibility of the information between the two conditions

Methods

Design

A single centre double blind randomised controlled trial, with a between participants design was conducted at the Wellcome Trust King's Clinical Research Facility in the UK. This study was approved by the Psychiatry, Nursing and Midwifery Research Ethics Subcommittee at King's College London (Reference number: PNM 14/15-62).

Participants

Participants who were healthy, aged 18 or over, and fluent in English were invited to take part. Participants with chronic or acute illnesses which were currently symptomatic or those who were pregnant or breast feeding were excluded to prevent any interference with symptom reporting. Participants were asked to list any allergies to medicines and/or the inactive ingredients often found in them. Examples of the potential inactive ingredients were given and these covered all the ingredients in the tablet. Participants who listed allergies to any of the substances in our tablet were also excluded. Participants who had taken any pain killers within 4 hours before taking part, or who had been drinking alcohol on the day of participation were rescheduled.

Procedure

Participants were recruited through adverts on university circular emails and posts on GumTree. These adverts presented an outline of the study, inclusion criteria and an email address to contact us for further information. Interested participants were emailed an information sheet and screening questionnaire. The information sheet explained that the study aim was to "assess the severity of short-term side effects to a well-known tablet." It explained that we could not tell participants what the tablet is or what it is used for as we "do not want

to bias your views about it", and that the tablet would be referred to in written materials as "XXXXXXX". The information sheet explained that the tablet has been shown to have beneficial effects for people and that no prescription is needed to take it. It stated that the tablet can cause short term side effects, and that we wanted to assess how severe these side effects are. The information sheet also explained that as part of the study we would randomise participants to receive one of two PILs that have been developed for this tablet to see if they influence what people think about it. Participants were told that the only difference between the two PILs was small changes to the wording, but that we could not tell them what would be changed.

Eligible participants arranged a time with the researcher to participate. After booking in at the reception of the clinical research facility, they were led to a fully equipped testing room where a researcher double-checked the participants' screening questionnaire. Participants were asked to give written consent. Given the nature of the research, consent was not fully informed, although participants were aware that information was being withheld from them. After providing consent, participants answered questions about demographics, recent symptoms, and anxiety. Participants were randomised to receive one of two leaflets about the tablet which they read immediately. The leaflets were sealed in an opaque envelope. Participants were given as long as they needed to read the leaflet once before putting it back in the envelope. They then answered questions about the credibility of the information in the leaflets and their anxiety. Once these questions were completed participants took the tablet with water. Over the next hour, they completed a variety of vigilance and cognitive tasks, chosen to enhance the appearance that this was a formal clinical trial for a drug. In reality, data from these 'filler' tasks were discarded. Participants then completed questions about their symptom experience, their anxiety, and what they thought the tablet was. All participants received £40 for taking part via shopping vouchers or

bank transfer. After all participants had been tested, we contacted participants to explain the real nature of the study and to provide an opportunity to withdraw their data if they wished: none did. A summary of the procedure can be been seen in Figure 1. The inert tablet was manufactured by Guy's and St Thomas Pharmacy and was stored and dispensed at the Pharmacy Department at Maudsley Hospital.

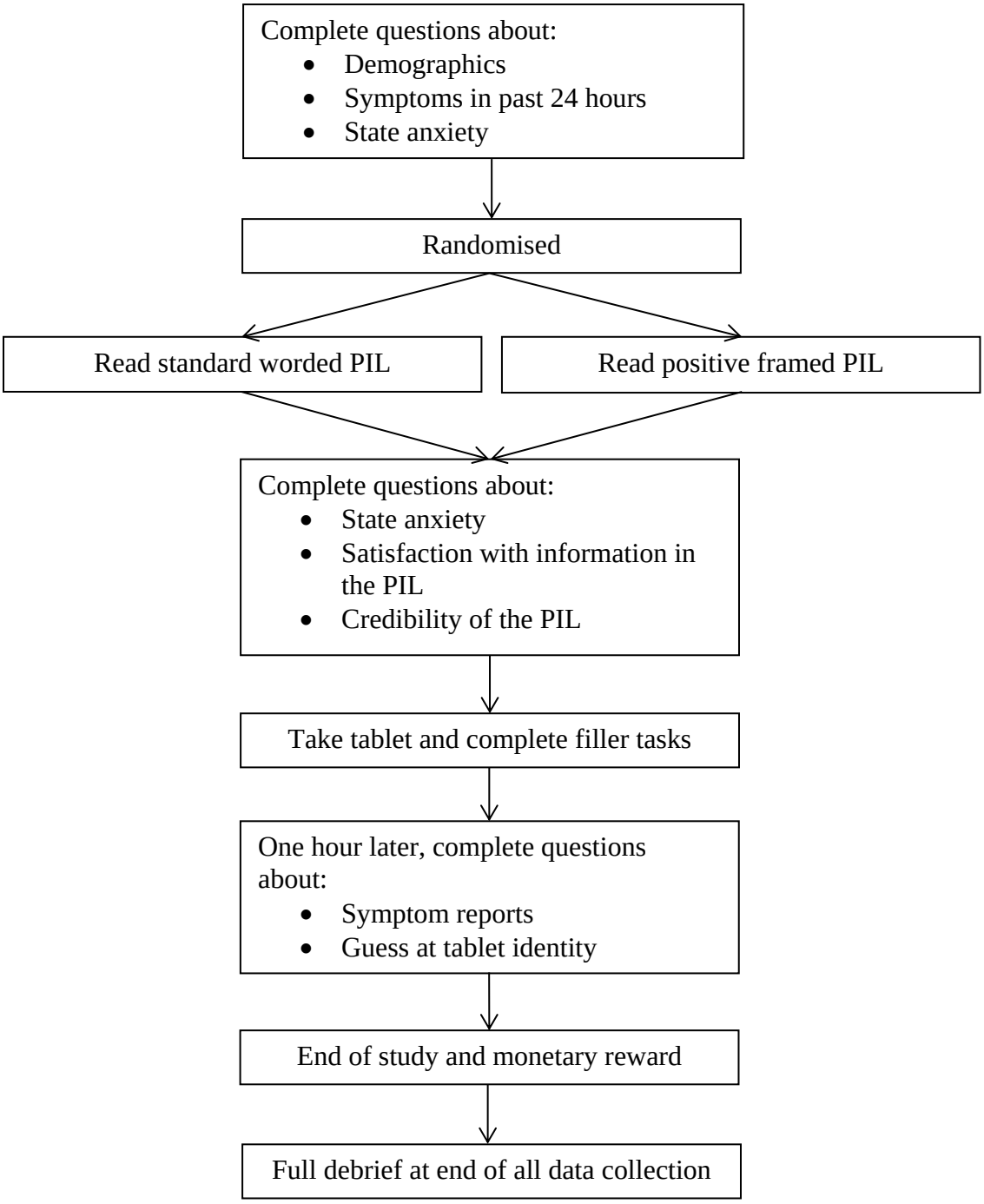

Figure 1. Study procedure

Measures

At baseline we included demographic questions relating to: age, gender, ethnicity, highest level of education, and employment status. Symptoms in the past 24 hours were measured using the generic assessment of side effects (GASE) scale (22). The GASE is an instrument used to assess side effects in clinical trials and supports the early detection of

drug-induced adverse events. We modified the scale so that 23 symptoms were selected according to those commonly reported during a nocebo response and those listed on the GASE that could be detected within an hour of taking the tablet, and were not too serious (e.g. headache, dizziness, itchy skin). Fourteen of these symptoms were mentioned on the PILs (headache, nausea, cough, dizziness, pain in limb, runny nose, sore throat, stomach ache, tiredness, bloating, itchy skin, confusion, agitation, anxiety) and nine were not (chest pain, hot flushes, depressed mood, dry mouth, abnormal sweating, breathing problems, tremor, palpitation, irritability). Participants rated each symptom on a four point scale ranging from "not present" to "severe". State anxiety was measured using the State Anxiety Inventory- short version (23). This includes six items which participants rated on a four point scale ranging from "not at all" to "very much". Internal consistency of the scale is high with a Cronbach's alpha of 0.82.

After reading the PIL, satisfaction was measured using seven statements about the clarity of the information, the type of information provided and overall satisfaction, which participants rated on a five point scale ranging from "strongly disagree" to "strongly agree", and we included a measure of their state anxiety again. To assess the credibility of the PIL we used the Myers credibility index (18). Participants rated the information in the PIL on 5 continuums: trust, accuracy, fairness, bias and disclosure, using a 5 point scale from 1-5. Participants' state anxiety was also measured again after they read the PIL.

After taking the tablet, we measured participants' symptom reports using a different modification of the GASE, with participants asked to rate each symptom on a four point scale ranging from "not present" to "severe", and asked if any symptom they experienced was related to taking the tablet ("yes" or "no"). Finally, participants were asked to give their best guess at what the tablet was and to rate how confident they were about this on a scale from 1-5.

Intervention

The intervention was based on positively framing side effect risk as a way to reduce participant's expectations of side effects, making them less likely to be reported. The intervention was delivered through the means of a PIL printed on an A4 sheet of paper given to participants by the researcher in a sealed envelope. Participants could receive a standard worded PIL akin to those used in current practice, or the intervention PIL. The leaflets were designed to be accurate for an inert tablet, providing information on what might be expected solely as a result of placebo or nocebo effects. As participants were not told what the tablet was, certain sections of the PIL were redacted, with text replaced by a single, large "X"; these included the sections: 'What XXXXXXX is and what it is used for,' 'other medicines and XXXXXXX,' 'recommended doses,' and 'what XXXXXXX contains.' The only difference between the two leaflets was the 'possible side effects' section. The standard worded PIL followed current guidelines for describing side effect risk, e.g. 'Common side effects (1 in 10 people will be affected).' The intervention PIL applied positive framing to the risks, by rewording the verbal descriptor, presenting the number of people who would not be affected and using percentages which have previously been shown to elevate perceptions of likelihood compared to natural frequencies (24). For copies of the leaflets see the electronic supplemental material. Pilot testing in a randomised controlled cross-over trial (n=30) provided preliminary data that the intervention was effective in changing expectations.

Randomisation and masking

Randomisation was carried out by the King's Clinical Trial Unit (KCTU) using randomly varying block sizes, stratified by gender. Participants' details were entered onto an online randomisation system provided by KCTU after they gave consent and an email was immediately sent back to the researcher providing a unique envelope number to give to the participant. The envelope contained either the standard worded or positively framed PIL. The

envelopes were opaque and were pre-packed and sealed in advance by a separate member of the team. The researcher was blind to the contents of the envelope. Participants were not told the difference between the two leaflets.

Outcomes

Our primary outcomes were the number of participants who reported one or more symptoms which they attributed to the tablet; the number of symptoms attributed to the tablet; and the severity of symptoms attributed to the tablet.

In a change to our registered protocol, we decided to include satisfaction and credibility scores for the two leaflets as secondary outcomes.

Statistical analysis

The sample size calculation was based on the assumption that 25% of participants in the control condition would develop symptoms (3), and that we were interested in reducing this to 10% or lower. To detect this effect as significant at $p < .05$ with 80% power, using a z-test for independent proportions, 100 participants were required in each group

Following consultation with a biostatistician, in a change to our registered protocol we used a hurdle model to assess the effect of the intervention on number of participants attributing symptoms to the tablet and the number of symptoms attributed to the tablet. This consisted of a joint logistic and truncated negative binomial regression. This is a more powerful analysis to use for count data when there is an excess number of zeros than would be expected by a negative binomial regression. The logistic regression identified the effect of leaflet condition on the odds of participants experiencing symptoms as opposed to not experiencing symptoms, whilst the truncated negative binomial regression identified the effect of leaflet condition on the rate of symptoms attributed to the tablet. Due to the effect that baseline symptoms could have on symptom reporting at follow-up due to misattribution

(25,26), we controlled for baseline symptoms in these analyses to give a more accurate result for the effect of leaflet condition on reported symptoms. As symptom severity was based on scale data, and had a non-normal distribution the effect of the intervention on the severity of symptoms that were attributed to the tablet were analysed using Mann-Whitney U tests. These analyses were conducted separately for symptoms which were mentioned in the PIL and for symptoms not mentioned in the PIL. For completeness we also included an analysis of all attributed symptoms, which included both symptoms that were mentioned in the PIL and those that were not mentioned in the PIL.

For the secondary outcomes due to non-normal distributions the difference in satisfaction and credibility scores between the PILs was examined using Mann-Whitney U tests.

Due to the influence that baseline anxiety has had on previous experimental studies in nocebo research e.g. (27), we carried out a post-hoc analysis using logistic regression, controlling for the number of baseline symptoms to assess the interaction between the leaflets participants were randomised to receive and baseline anxiety to see if this influenced the odds of participants attributing any symptom to the tablet.

Because of a computer failure, which resulted in data for one participant being irretrievably lost, and because we excluded data from the first two participants whom we used as pilot runs for the study, our clinical trials unit advised us to recruit an additional six participants to ensure the eventual sample size would exceed 100 in each arm. Data for 203 participants were therefore included in the analyses. All analyses were carried out using SPSS version 24.0, apart from the hurdle model which was carried out using Stata version 15.

Trial registration: ISRCTN47470030

Results

Participants were recruited between Dec 1, 2015 to Dec 5, 2016.The final sample contained 203 participants, 101 assigned to the standard worded PIL, and 102 assigned to the positively framed PIL (see Figure 2 for participant flow). The mean age of the sample was 27.15 years. Participants consisted of 65 men and 138 women with the majority being of white ethnicity (59.6%). For full baseline characteristics see Table 1.

Table 1. Baseline characteristics of the sample

Variable	Standard worded PIL (n = 101)	Positively framed PIL (n = 102)	Total sample (N = 203)
Age	27.28 (8.69)	27.03 (8.61)	27.15 (8.63)
Gender			
Male	32 (31.7%)	33 (32.4%)	55 (32.0%)
Female	69 (68.3%)	69 (67.6%)	138 (68.0%)
Ethnicity			
White	65 (64.4%)	56 (54.9%)	121 (59.6%)
Other	36 (35.6%)	46 (45.1%)	82 (40.4%)
Education			
Secondary school	37 (36.6%)	34 (33.3%)	71 (35.0%)
Higher education	64 (63.4%)	68 (66.7%)	132 (65.0%)
Employment			
Working	45 (44.6%)	33 (32.4%)	78 (38.4%)
Not working	56 (55.4%)	69 (67.6%)	125 (61.6%)
Number of baseline symptoms	2.38 (2.51)	2.81 (2.87)	2.60 (2.60)
Severity of baseline symptoms	2.65 (2.94)	3.24 (3.59)	2.95 (3.29)
Baseline anxiety	9.51 (2.58)	9.69 (2.84)	9.60 (2.71)

Note: Data are n (%) or mean (SD), PIL = patient information leaflet

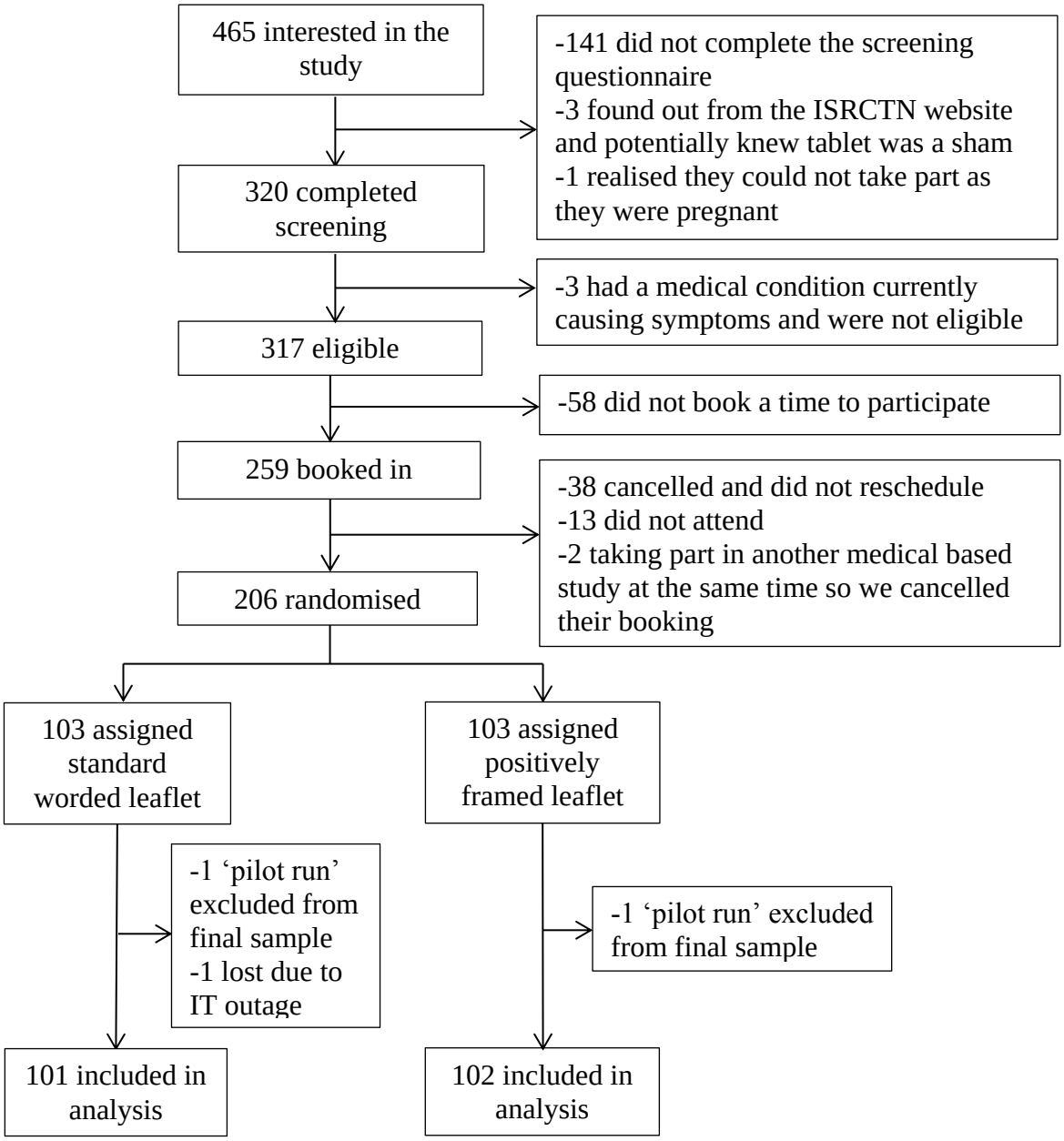

Figure 2. Trial profile

Note: Due to the loss of three participants from the sample, our clinical trials unit advised we recruited an extra six participants to ensure 100 in each arm as we did not know which leaflets the three participants had been assigned

Primary outcomes: symptom attribution

Table 2 shows the results from the primary outcome of the number of people who attributed symptoms to the tablet. Fifty (54.5%) participants who received the standard worded PIL experienced symptoms which they attributed to the tablet, compared with 40 (39.2%) participants who received the positively framed PIL. In other words participants who received the positively framed PIL were 34% (OR = 0.66) less likely to attribute symptoms to the tablet than participants who received the standard worded PIL, whilst adjusting for number of baseline symptoms. Similarly, participants who received the positively framed PIL were 34% (OR = 0.66) less likely to attribute symptoms mentioned in the PIL to the tablet than participants who received the standard worded PIL. There was no difference in the odds of attributing symptoms not mentioned in the PIL to the tablet. There was no significant difference between the leaflets for the number (all p values > .067) and severity (all p values > .149) of symptoms reported that were attributed to the tablet, see Table 2.

Secondary outcomes: satisfaction and credibility scores

There was no significant difference between the leaflets in terms of satisfaction with or credibility of the PILs (see Table 3). Both leaflets scored well for both outcomes. In addition there was no difference in anxiety scores after reading either leaflet.

Table 2. The difference in symptom reporting between the two leaflets

Outcome	Standard worded PIL (n = 101)	Positively framed PIL (n = 102)	Test*	Effect size (95% CI)
Symptoms mentioned in PIL				
Experienced	47 (46.5%)	33 (32.4%)	z = -2.25	OR = 0.66
Did not experience	54 (53.5%)	69 (67.6%)	p = .024	(0.46-0.95)
Number of symptoms	0.72 (0.92)	0.69 (1.06)	z = 1.83 p = .067	RR = 1.22 (0.99-1.50)
Severity of symptoms	0.78 (1.05)	0.78 (1.43)	*U* = 4645.0 p = .168	r = - 0.10
Symptoms not mentioned in PIL				
Experienced	24 (23.8%)	22 (21.6%)	z = -0.52	OR = 0.90
Did not experience	77 (76.2%)	80 (78.4%)	p = .606	(0.61-1.33)
Number of symptoms	0.32 (0.65)	0.33 (0.71)	z = 0.73 p = .467	RR = 1.09 (0.86-1.34)
Severity of symptoms	0.38 (0.83)	0.40 (0.95)	*U* = 5063.0 p = .774	r = - 0.02
Any symptoms				
Experienced	55 (54.5%)	40 (39.2%)	z = -2.35	OR = 0.66
Did not experience	46 (45.5%)	62 (60.8%)	p = .019	(0.46-0.93)
Number of symptoms	1.04 (1.22)	1.01 (1.73)	z = 1.45 p = .148	RR = 1.19 (0.94-1.50)
Severity of symptoms	1.16 (1.46)	1.21 (2.14)	*U* = 4596.5 p = .149	r = - 0.10

Note: Data are n (%) or mean (SD), OR = Odds ratio, RR = rate ratio, PIL = patient information leaflet, * = all adjusted for number of baseline symptoms apart from symptom severity tests, r = pearson's correlation which can be calculated from Mann-Whitney U output. 95% CI for r is not able to be calculated from Mann-Whitney U output.

Table 3. The difference in satisfaction and credibility median scores between the two leaflets

Outcomes	Standard worded PIL (n = 101)	Positively framed PIL (n = 102)	Test	Effect size
Satisfaction				
Leaflet was clear	4.0 (4.0-5.0)	4.0 (4.0-5.0)	*U* = 5024.5 p = .730	r = - 0.02
Leaflet was easy to understand	4.0 (4.0-5.0)	4.0 (4.0-5.0)	*U* = 4971.0 p = .617	r = - 0.04
Leaflet contained words I did not understand	1.0 (1.0-2.0)	1.0 (1.0-2.0)	*U* = 5021.0 p = .718	r = - 0.03
Leaflet was similar to other leaflets	4.0 (4.0-5.0)	4.0 (4.0-5.0)	*U* = 4934.5 p = .557	r = - 0.04
There was enough information to make an informed choice	3.0 (3.0-5.0)	4.0 (4.0-4.0)	*U* = 5118.5 p = .932	r = - 0.01
There was sufficient information about the risks and benefits	4.0 (4.0-5.0)	4.0 (4.0-5.0)	*U* = 4980.5 p = .642	r = - 0.03
Overall I am satisfied with the leaflet	4.0 (4.0-5.0)	4.0 (4.0-5.0)	*U* = 4870.0 p = .451	r = - 0.05
Anxiety after reading the leaflet	9.0 (8.0-11.0)	9.0 (7.75-11.25)	*U* = 5037.0 p = .783	r = - 0.02
Credibility				
Trustworthy	4.0 (4.0-5.0)	4.0 (4.0-4.0)	*U* = 4691.0 p = .202	r = - 0.09
Accurate	4.0 (4.0-4.0)	4.0 (4.0-4.0)	*U* = 5003.0 p = .690	r = - 0.02
Fair	4.0 (4.0-4.0)	4.0 (4.0-4.0)	*U* = 5126.0 p = .946	r = - 0.01
Tells the whole story	3.0 (3.0-4.0)	3.0 (3.0-4.0)	*U* = 5096.5 p = .892	r = - 0.01
Unbiased	4.0 (3.0-4.0)	4.0 (3.0-4.0)	*U* = 4639.5 p = .191	r = - 0.09

Note: Data are median (IQR), PIL = patient information leaflet, pearson's correlation r has been calculated as an effect size from Mann-Whitney U output. 95% CI for r is unable to be calculated from Mann-Whitney U output.

Post-hoc analysis

For the post-hoc analysis there was no significant interaction between the leaflet type and participants' baseline anxiety scores, controlling for number of baseline symptoms, OR = 1.056, p = .054, 95% CI [0.999 to 1.116].

Guess at tablet identity

The majority (49.8%) of participants thought the tablet was an over the counter analgesic such as paracetamol, ibuprofen, or aspirin. Nearly a third of participants (31.5%) did not know what the tablet was. Participants' confidence in their guesses as to tablet identify was low, with a mean score of 1.88 out of 5 for participants who did not give an answer of 'Don't know'. Only 9 participants guessed that the tablet was a sham, with the mean confidence of participants who guessed this being low (2.22 out of 5). Five of these received the standard worded PIL and four received the positively framed PIL.

Sensitivity analyses

Excluding the nine participants who guessed it was a placebo from the analyses did not change the outcome of any of the results, apart from the post-hoc analysis. In this instance for each one point increase in baseline anxiety score participants were 1.06 times as likely to experience symptoms if they received the standard worded PIL compared to the positively framed PIL. See supplementary material for full results of sensitivity analyses.

Discussion

The results from this study show that positive framing of side effect information reduces the likelihood of participants experiencing symptoms which they attribute to a recently taken tablet. This reduction is clearly linked to the phrasing used in the leaflet – it applies only to those symptoms described in the leaflet and not to others. This finding supports previous work showing the effectiveness of positive framing of side effect information in reducing side effect reporting following influenza vaccination (20). Despite

previous claims that positive framing might be seen as a marketing ploy by patients (21), there was no difference in participant satisfaction for the two leaflets or their perceived credibility.

This was a well-controlled and adequately powered study, with both participants and researcher blind to the experimental condition. Although nine participants guessed the tablet was a sham, the most common reason given for this was because they did not experience any effects from the tablet. Only two participants who guessed it was an inert tablet suggested this because they thought we were testing how side effect information affected symptom development, although both had low confidence in their guess. This shows the strength of the model used here for work on the nocebo effect and supports the credibility of the study. Although ethical issues are raised through the use of deception to elicit symptoms in participants, the information we gave to participants was accurate, in that it correctly conveyed what we know about placebo and nocebo effects. In addition we made participants aware that information was being withheld from them, thereby using an 'authorised deception' approach to consent. Our method was well received by participants. At the end of data collection participants were emailed a debrief explaining the study aims. Sixteen participants replied, expressing pleasant surprise and interest. No-one responded negatively.

One limitation inherent in our design was that participants were more focussed on monitoring themselves for symptoms than they might have been in daily life after taking a tablet. Although we attempted to reduce this effect by occupying participants with cognitive tasks after taking the tablet, this effect is likely to have raised levels of symptom reporting in both experimental conditions. Other limitations include the fact that our sample was not representative of the general public, in particular being well-educated, with 65% having a higher education qualification, and young, with a mean age of 27. Also, as participants volunteered knowing that we were investigating side effects to a tablet, it is possible that

those who volunteered were people who were generally trusting of medications or medical science. This could explain why no interaction was found between baseline anxiety and leaflet type, as participants' anxiety was already quite low. Given that these factors may reduce the likelihood of nocebo effects occurring, the number of participants who attributed symptoms to our tablet, and the number and severity of these attributed symptoms is likely to be an underestimate compared to the general public.

Another limitation concerns the fact that we altered two parts of the side effect information in the intervention PIL – the numeric and verbal risk information. This means we cannot tell if only one part is causing the effect or if there is a cumulative effect of the numeric and verbal information. Further study is needed to explore this. In addition our follow-up period of one hour may have been a limitation. It is possible that a longer follow-up may have altered the results in different ways. For example participants may have been more likely to experience unrelated physical symptoms and misattribute them to the tablet, or it may be that the framing manipulation would have worn off after a longer period of time.

Our findings suggest that framing the risk of side effects in PILs positively in terms of those who will remain side effect free has the potential to reduce the risk of nocebo induced side effects that patients experience to their medications. There would be no financial cost to implementing the intervention, which could be easily introduced throughout the healthcare system. Importantly it does not infringe participants' ability to give fully informed consent, something which has been a concern about previous proposed interventions (28). Nonetheless it is important for future research to test the effectiveness of positive framing in a more realistic situation, for example with patients with clinical conditions prescribed real medication. Two issues in particular require further attention. First, does positive framing reduce the likelihood of patients reporting severe side effects to their physician? This would be undesirable if so. Second, is the intervention only effective in the short term? It is possible,

for example, that over a longer period of time patients will forget the information in the leaflet, reducing the impact of the positive framing.

Nocebo induced side effects attributed to medications result in a significant cost to the NHS and to patients' quality of life. Positive framing of side effect information in PILs appears to be a cheap, effective intervention to reduce the risk of this occurring, and does not affect patients' ability to give fully informed consent. Future work is needed to assess the effectiveness in a more realistic setting.

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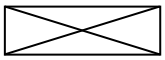
Supplementary material:
Standard worded leaflet

Package Leaflet: Information for the user

XXXXXXX hard tablets

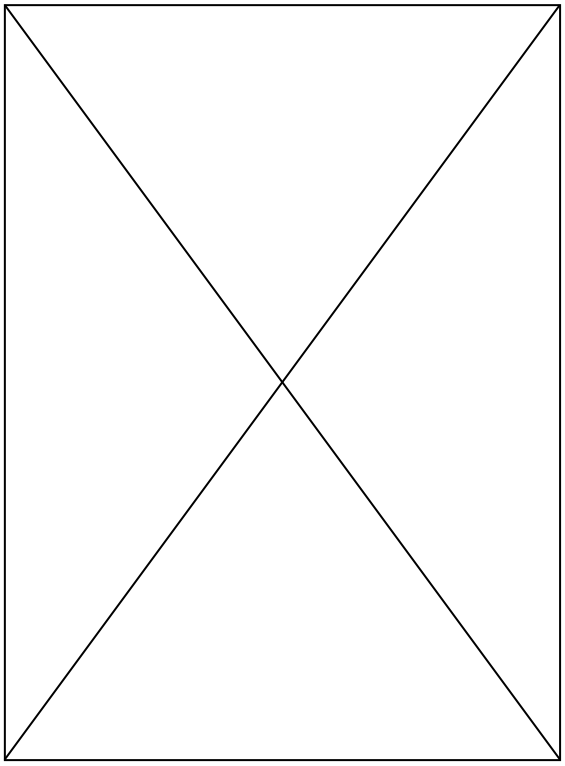


Read this leaflet carefully because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What XXXXXXX is and what it is used for



2. What you need to know before you take XXXXXXX

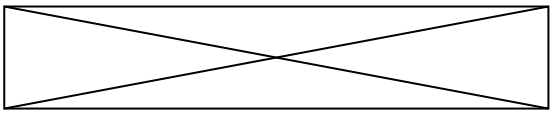
Do not take XXXXXXX:

- **if you are allergic** to any of the ingredients of XXXXXXX listed in section 6.

Warnings and precautions:
Before you take XXXXXXX, talk to your doctor

- if you are **allergic to other over-the-counter tablets**
- If you have **diabetes**
- if you have a **severe medical condition**, which may require immediate hospitalisation

Other tablets and XXXXXXX



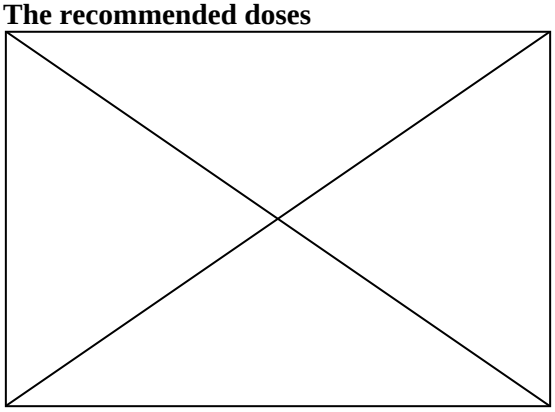
Pregnancy and breast-feeding
XXXXXXX has no known effect on pregnant women, women trying to conceive or on breast-fed infants.

Driving and using machines
XXXXXXX has been known to have an effect on your ability to drive or use machines due to the occurrence of possible side effects. If you are affected do not drive or use machines until the side effects wear off.

3. How to take XXXXXXX

Take this tablet exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended doses



Method of administration
Swallow the tablet with water. The tablet can be divided into two equal halves.
Do not chew the tablet.
XXXXXXX can be taken with or without food. But it is recommended to be taken without food to achieve the greatest effect.

If you take more XXXXXXX than you should
Stop taking XXXXXXX.
In most cases of overdose, people have reported an increased number and severity of side effects. When side effects were reported, they were similar to those from normal doses, as listed in section 4.

If you forget to take XXXXXXX
Take the next tablet as soon as you remember.

4. Possible side effects

Like all tablets, this tablet can cause side effects, although not everybody gets them. These side effects mostly occur within one hour after taking the first tablet and will usually stop as you continue to take them.

Very common side effects
(More than 1 in 10 people will be affected)
- Headache
- Nausea

Common side effects
(1 in 10 people will be affected)
- Cough
- Dizziness
- Pain in limb
- Runny nose
- Sore throat
- Stomach ache
- Tiredness
- Bloating

Uncommon side effects
(1 in 100 people will be affected)
- Itchy skin

Rare side effects
(1 in 1,000 people will be affected)
- Confusion
- Agitation
- Anxiety

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet.

5. How to store XXXXXXX

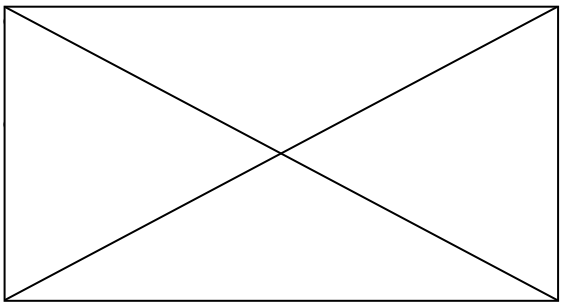
Keep out of the sight and reach of children.
Do not use this tablet after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Do not store above 25 °C.

Do not throw away any tablets via wastewater or household waste. Ask your pharmacist how to throw away tablets you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What XXXXXXX contains



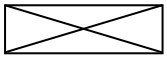
What XXXXXXX looks like
The tablets have a round white opaque body with a breakline.

This leaflet was last revised in 08/2015

<u>Supplementary material:</u>
<u>Positively framed leaflet</u>

Package Leaflet: Information for the user

XXXXXXX hard tablets

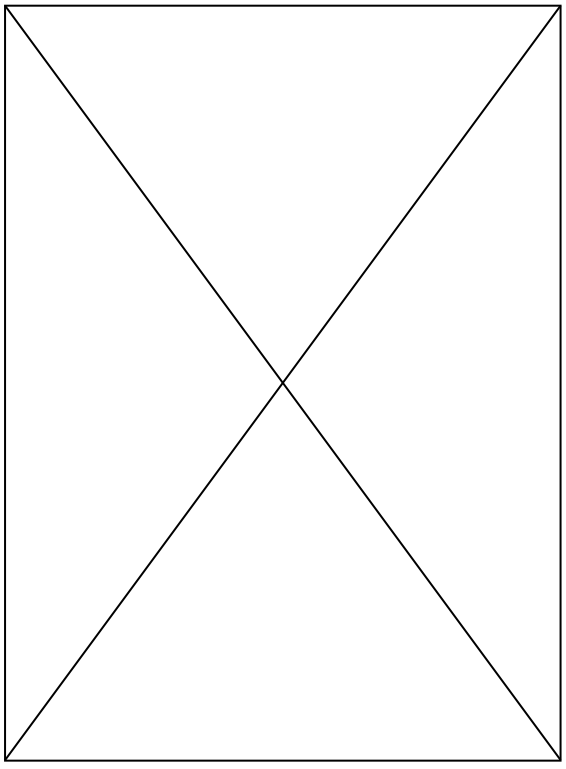


Read this leaflet carefully because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What XXXXXXX is and what it is used for



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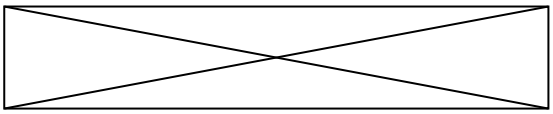
Warnings and precautions:
Before you take XXXXXXX, talk to your doctor

- if you are **allergic to other over-the-counter tablets**
- If you have **diabetes**
- if you have a **severe medical condition**, which may require immediate hospitalisation

Other tablets and XXXXXXX



Pregnancy and breast-feeding
XXXXXXX has no known effect on pregnant women, women trying to conceive or on breast-fed infants.

Driving and using machines
XXXXXXX has been known to have an effect on your ability to drive or use machines due to the occurrence of possible side effects. If you are affected do not drive or use machines until the side effects wear off.

3. How to take XXXXXXX

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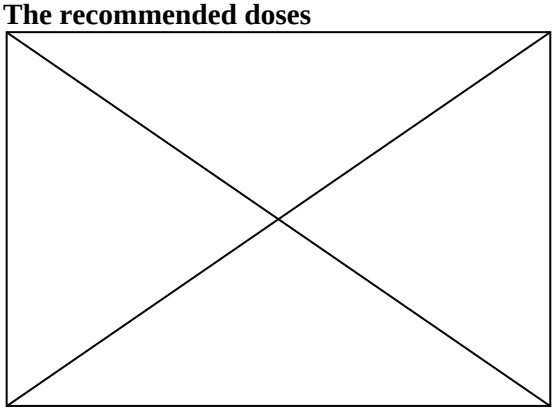
The recommended doses



Method of administration
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XXXXXXX can be taken with or without food. But it is recommended to be taken without food to achieve the greatest effect.

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In most cases of overdose, people have reported an increased number and severity of side effects. When side effects were reported, they were similar to those from normal doses, as listed in section 4.

If you forget to take XXXXXXX
Take the next tablet as soon as you remember.

4. Possible side effects

Like all tablets, this tablet can cause side effects, although not everybody gets them. These side effects mostly occur within one hour after taking the first tablet and will usually stop as you continue to take them.

Uncommon side effects
(80% of people will not be affected)
- Headache
- Nausea

Very uncommon side effects
(90% of people will not be affected)
- Cough
- Dizziness
- Pain in limb
- Runny nose
- Sore throat
- Stomach ache
- Tiredness
- Bloating

Rare side effects
(99% of people will not be affected)
- Itchy skin

Very rare side effects
(99.9% of people will not be affected)
- Confusion
- Agitation
- Anxiety

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet.

5. How to store XXXXXXX

Keep out of the sight and reach of children.
Do not use this tablet after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

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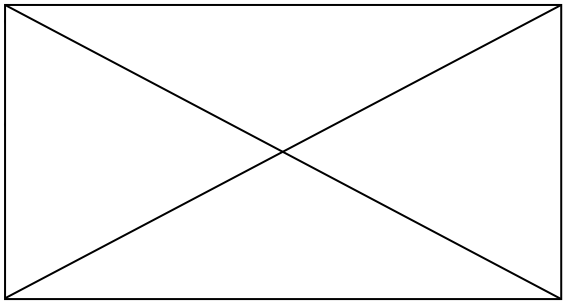

What XXXXXXX looks like
The tablets have a round white opaque body with a breakline.

This leaflet was last revised in 08/2015

Supplementary material: Sensitivity analyses - rerunning analyses without the 9 participants who guessed that the tablet was a placebo

The difference in symptom reporting between the two leaflets

Outcome	Standard worded PIL (n = 96)	Positively framed PIL (n = 98)	Test*	Effect size (95% CI)
Symptoms mentioned in PIL				
Experienced	46 (47.9%)	33 (33.7%)	z = -2.25	OR = 0.66
Did not experience	50 (52.1%)	65 (66.3%)	p = .024	(0.46-0.95)
Number of symptoms	0.75 (0.93)	0.69 (1.20)	z = 1.69 p = .091	RR = 1.20 (0.97-1.48)
Severity of symptoms	0.81 (1.06)	0.82 (1.45)	*U* = 4247.5 p = .187	r = - 0.09
Symptoms not mentioned in PIL				
Experienced	24 (25.0%)	21 (21.4%)	z = -0.82	OR = 0.85
Did not experience	72 (75.0%)	77 (78.6%)	p = .411	(0.57-1.26)
Number of symptoms	0.33 (0.66)	0.35 (0.79)	z = 0.76 p = .449	RR = 1.10 (0.86-1.39)
Severity of symptoms	0.40 (0.85)	0.41 (1.06)	*U* = 4565.5 p = .631	r = - 0.03
Any symptoms				
Experienced	54 (56.3%)	39 (39.8%)	z = -2.54	OR = 0.63
Did not experience	42 (43.8%)	59 (60.2%)	p = .011	(0.43-0.90)
Number of symptoms	1.08 (1.23)	1.04 (1.75)	z = 1.42 p = .155	RR = 1.19 (0.94-1.51)
Severity of symptoms	1.21 (1.48)	1.23 (2.17)	*U* = 4162.0 p = .1433	r = - 0.12

Note: Data are n (%) or mean (SD), OR = Odds ratio, RR = rate ratio, PIL = patient information leaflet, * = all adjusted for number of baseline symptoms apart from symptom severity tests, r = pearson's correlation which can be calculated from Mann-Whitney U output. 95% CI for r is not able to be calculated from Mann-Whitney U output.

The difference in satisfaction and credibility median scores between the two leaflets

Outcomes	Standard worded PIL (n = 96)	Positively framed PIL (n = 98)	Test	Effect size
Satisfaction				
Leaflet was clear	4.0 (4.0-5.0)	4.0 (4.0-5.0)	*U* = 4571.0 p = .700	r = - 0.03
Leaflet was easy to understand	4.0 (4.0-5.0)	4.0 (4.0-5.0)	*U* = 4467.5 p = .485	r = - 0.05
Leaflet contained words I did not understand	1.0 (1.0-2.0)	1.0 (1.0-2.0)	*U* = 4553.5 p = .655	r = - 0.03
Leaflet was similar to other leaflets	4.0 (4.0-5.0)	4.0 (4.0-5.0)	*U* = 4476.0 p = .509	r = - 0.05
There was enough information to make an informed choice	4.0 (3.0-5.0)	4.0 (4.0-4.0)	*U* = 4568.0 p = .705	r = - 0.03
There was sufficient information about the risks and benefits	4.0 (4.0-5.0)	4.0 (4.0-5.0)	*U* = 4485.5 p = .526	r = - 0.05
Overall I am satisfied with the leaflet	4.0 (4.0-5.0)	4.0 (4.0-5.0)	*U* = 4344.5 p = .305	r = - 0.07
Anxiety after reading the leaflet	9.0 (8.0-11.0)	9.0 (7.0-11.0)	*U* = 4555.0 p = .700	r = - 0.03
Credibility				
Trustworthy	4.0 (4.0-5.0)	4.0 (4.0-4.0)	*U* = 4250.5 p = .177	r = - 0.09
Accurate	4.0 (4.0-5.0)	4.0 (4.0-4.0)	*U* = 4546.0 p = .646	r = - 0.03
Fair	4.0 (4.0-4.0)	4.0 (4.0-4.0)	*U* = 4615.0 p = .797	r = - 0.02
Tells the whole story	3.0 (3.0-4.0)	3.0 (3.0-4.0)	*U* = 4685.5 p = .961	r = - 0.004
Unbiased	4.0 (3.0-4.0)	4.0 (3.0-4.0)	*U* = 4156.0 p = .133	r = - 0.12

Note: Data are median (IQR), PIL = patient information leaflet, pearson's correlation r has been calculated as an effect size from Mann-Whitney U output. 95% CI for r is unable to be calculated from Mann-Whitney U output.

Post-hoc analysis

There was a significant interaction between the leaflet type and participants' baseline anxiety scores, controlling for number of baseline symptoms, OR = 1.06, p = .037, 95% CI [1.004 to 1.124]. For each one point increase in baseline anxiety score participants were 1.06 times as likely to experience symptoms if they received the standard worded PIL compared to the positively framed PIL.